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Neuro-endocrine mechanism of specific balneoeffects of sulfate-chloride sodium-magnesium mineral waters

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Background. Earlier we showed that the newly created sulfate-chloride sodium-magnesium drinking mineral waters "Myroslava" (5 g/L) and "Khrystyna" (10 g/L) have favorable effects on neuroendocrine-immune complex and metabolism of patients with their violations. At the same time, the influence of both waters on one constellation of parameters is similar, despite the twofold difference in mineralization, while on the other constellation it is different. The aim of this study was to elucidate the neuroendocrine mechanism of specific effects. **Materials and Methods**. The object of clinical-physiological observation were 22 men aged 23-70 years, who underwent rehabilitation treatment of chronic pyelonephritis and cholecystitis in remission in the Truskavets' spa. The examination was performed twice, before and after a 7-10-day course of balneotherapy. All patients received bioactive water Naftussya, however, 11 men additionally drank water "Khrystyna", and the other 11 men - water "Myroslava". The subject of the study were the parameters of the neuroendocrine-immune complex and metabolism. **Results**. The method of canonical analysis shows that the changes in neuroendocrine factors (LF and VLF bands HRV; beta- and delta-rhythm-generating nerve structures, cortisol and aldosterone determine changes in the parameters of immunity, microbiota, metabolism and cholekinetics by 99,5-98,6%. **Conclusion**. The primary effects of mineral waters are the modulation of the activity of the structures of the central and autonomic nervous and endocrine systems, which, in turn, have a regulatory modulating effect on the immune system, microbiota, metabolism, cholekinetics and blood pressure.

Keywords: sulfate-chloride sodium-magnesium drinking mineral waters, Truskavets' spa, EEG, HRV, endocrine, immune, metabolic parameters, relationships.

INRODUCTION

Earlier we showed that the newly created sulfate-chloride sodium-magnesium drinking mineral waters "Myroslava" (5 g/L) and "Khrystyna" (10 g/L) have favorable effects on neuroendocrine-immune complex and metabolism of patients with their violations. At the same time, the influence of both waters on one constellation of parameters is similar [8,13,14], despite the twofold difference in mineralization, while on the other constellation it is different. Screening revealed specific changes in 37 parameters grouped into 5 patterns. The first pattern combines 11 parameters that decrease under the influence of "Myroslava" water (Myr), while increase under the influence of "Khrystyna" water (Khr). For the other 7 parameters of the second pattern, Myr acts similarly, while Khr is ineffective. Both mineral waters have a stimulating effect on 8 parameters, while Myr is inferior to Khr. Myr has a upregulating effect on 9 parameters of the fourth pattern, while Khr has a downregulating effect. Finally, sodium excretion and leukocyturia are reduced under the influence of both waters, but to a greater extent under the influence of Khr [25]. The aim of this study was to elucidate the neuroendocrine mechanism of specific effects.

MATERIALS AND METHODS

The object of clinical-physiological observation were 22 men aged 23-70 years, who underwent rehabilitation treatment in the Truskavets' spa of chronic cholecystitis and pyelonephritis in remission with of neuroendocrine-immune complex dysfunction. The examination was performed twice, before and after a 7-10-day course of balneotherapy. Patients received bioactive water Naftussya (3 ml/kg one hour before meals three times a day) and in half an hour additionally drank water "Khrystyna" or "Myroslava" in the same dose.

The day before, daily urine was collected, in which was determined the concentration of electrolytes: calcium (by reaction with arsenase III), magnesium (by reaction with colgamite), phosphates (phosphate-molybdate method), chloride (mercury-rhodanidine method), sodium and potassium (flamming photometry); nitric metabolites: creatinine (by Jaffe's color reaction by Popper's method), urea (urease method by reaction with phenolhypochlorite), uric acid (uricase method).

The same metabolic parameters were determined in plasma as well as glucose (glucose-oxidase method), triglycerides (by a certain meta-periodate method), total cholesterol (by a direct method after the classic reaction by Zlatkis-Zack) and content of him in composition of α-lipoproteins (by the enzyme method after precipitation of notα-lipoproteins); prae-β-lipoproteins (expected by the level of triglycerides); β-lipoproteins (expected by a difference between a total cholesterol and cholesterol in composition α-and prae-β-lipoproteins).

The analysis carried out according to instructions [6] with the use of analyzers "Reflotron" (BRD) and "Pointe-180" (USA) and corresponding sets of reagents.

We determined also content in plasma major hormones of adaptation: Cortisol, Aldosterone, Testosterone, Calcitonin and Triiodothyronine (by the ELISA with the use of analyzer "RT-2100C" and corresponding sets of reagents from "Алкор Био", XEMA Co., Ltd and DRG International Inc.).

In basal conditions we estimated the state of the autonomous regulation by the method heart rate variability (HRV) [2,4,10,32], using a hardware-programmatic complex "CardioLab+HRV" (KhAI Medica, Kharkiv, Ukraine).

Simultaneosly with HRV we recorded EEG a hardware-software complex "NeuroCom Standard" (KhAI MEDICA, Kharkiv) monopolar in 16 loci (Fp1, Fp2, F3, F4, F7, F8, C3, C4, T3, T4, P3, P4, T5, T6, O1, O2) by 10-20 international system, with the reference electrodes A and Ref tassels on the ears. The duration of the epoch was 25 sec [14].

We calculated also for each locus EEG Shannon's CE entropy (h) of normalized power spectral density (PSD) using Popovych's IL formula [9]:

$$hEEG = - [PSD\alpha \cdot \log_2 PSD\alpha + PSD\beta \cdot \log_2 PSD\beta + PSD\theta \cdot \log_2 PSD\theta + PSD\delta \cdot \log_2 PSD\delta]/\log_2 4$$

Immunity and microbiota status evaluated as described in the manuals [5,19] and in our previous works [9,13].

On the tone and motility of gall-bladder judged by its volume on an empty stomach in the morning and after 5, 15 and 30 min after ingestion cholekinetic (50 ml of 40% solution of xylitol). The method echoscopy (echocamera "Radmir") applicated [20-22]. To quantify cholekinetics, the area between the cholecystovolumogram and the basal line was calculated.

For statistical analysis used the software package "Statistica 64".

RESULTS AND DISCUSSION

Previous studies by the Truskavetsian Scientific School of Balneology have revealed significant correlations between EEG and HRV parameters [27,30], EEG and HRV, on the one hand, and leukocytogram [17], phagocytosis [16] and immunogram [15] - on the other hand, as well as between changes in these constellations under the influence of balneotherapy [18,28,29]. In addition, close neuroendocrine-metabolic and neuroendocrine-immune relationships have recently been found in healthy rats, both intact and exposed to water-salt loads [23].

These findings provide grounds for the hypothesis of the neuroendocrine mechanism of specific effects of mineral waters on the parameters of immunity, microbiota, metabolism, cholekinetics and diastolic pressure.

To test the hypothesis, previously identified discriminant variables were divided into two networks. Unfortunately, the program "Statistica 64" limits the number of parameters to 20 (n = 22 patients - 2). Two pairs of canonical roots are distinguished. The first set consisted of neuroendocrine parameters as factor (causal), and the second set - parameters of immunity, microbiota, metabolism, cholekinetics and diastolic pressure as effective, ie those whose changes are apparently the result of regulatory effects of causal parameters (Table 1).

Table 1. Matrix of correlations between changes in EEG&HRV&Endocrine and dependent parameters

Vari-ables	BP d	lg LU	lg EC	KI EC	Mon	Pop SI-1	CD3 TaL	Ig G	Ig M	Cr Ex	UA Ex	Na Ex	CCK Ind	Mg Ex
LF r	0,12	**0,43**	**-0,34**	**-0,42**	**0,43**	**0,41**	0,05	0,03	0,12	**0,41**	0,14	**-0,34**	**0,40**	-0,15
VLF r	-0,07	-0,14	-0,15	-0,02	**-0,34**	**-0,34**	-0,23	0,14	-0,03	-0,29	-0,08	**0,35**	**-0,46**	0,28
T5-β a	0,18	**0,35**	**-0,31**	-0,27	0,08	0,18	-0,07	-0,08	-0,22	0,14	**0,36**	**-0,39**	**0,63**	0,03
C3-δ a	-0,18	0,03	0,04	-0,20	-0,04	-0,17	-0,03	-0,07	**0,36**	-0,22	-0,29	0,25	**-0,53**	**-0,49**
Cortisol	-0,16	-0,00	-0,06	0,02	**-0,59**	**-0,34**	-0,23	-0,15	-0,04	0,01	-0,04	-0,20	**0,35**	-0,17
F8-β r	**0,32**	-0,04	0,01	0,12	-0,12	0,17	-0,06	-0,23	**-0,45**	0,11	0,26	**-0,44**	**0,36**	0,28
Aldost	0,03	0,15	-0,09	-0,04	0,00	0,03	-0,12	0,07	-0,02	**0,35**	0,03	-0,15	-0,04	-0,05

Note. According to the formula:

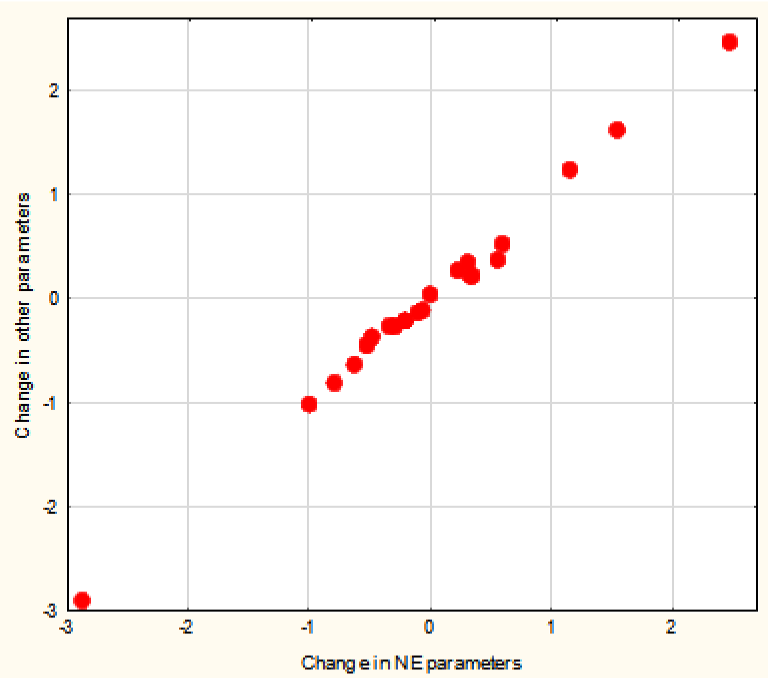
$$|r| \geq \{exp[2t/(n-1,5)^{0,5}] - 1\}/\{exp[2t/(n-1,5)^{0,5}] + 1\},$$

for a sample of 22 observations critical value of correlation coefficient module at $p<$**0,05** ($t>2,09$) is 0,431, at $p<$**0,02** ($t>2,53$) is 0,507, at $p<$**0,01** ($t>2,84$) is 0,556, at $p<$**0,001** ($t>3,85$) is 0,691.

The canonical correlation between the two sets of parameters was then analyzed. The factor structure of the first neuroendocrine root (Table 2) is formed by: inverse LF band HRV (reflects both sympathetic and vagal effects) and directly VLF band (its physiological essence is debatable [32]); beta-rhythm-generating nerve structures, probably [33], the left caudal anterior cortical cortex (inverse) and delta-rhythm-generating nerve structures, probably [31], the left hippocampus (directly), and plasma cortisol. Changes in these neuroendocrine factors determine changes in the parameters of immunity, microbiota, metabolism and cholekinetics by 99,5% (Fig. 1).

Table 2. Factor loads on the first pair of canonical roots

Neuro-Endocrine Variables	R 1
LF, %	-0,823
T5 β, PSD, μV²/Hz	-0,536
VLF, %	0,559
Cortisol	0,489
C3-δ PSD, μV²/Hz	0,175
Dependent Variables	**R 1**
Monocytes, %	-0,643
Popovych's Strain Index-1	-0,469
Leukocyturia, lgLeu/L	-0,435
Creatinine Excretion, mM/24 h	-0,354
Cholecystokinetic Index, units	-0,298
Ig G Serum, g/L	-0,211
Uric acid Excretion, mM/24 h	-0,200
Killing Index vs E. coli, %	0,421
Escherichia coli feces, lgCFU/g	0,375
Sodium Excretion, mM/24 h	0,141



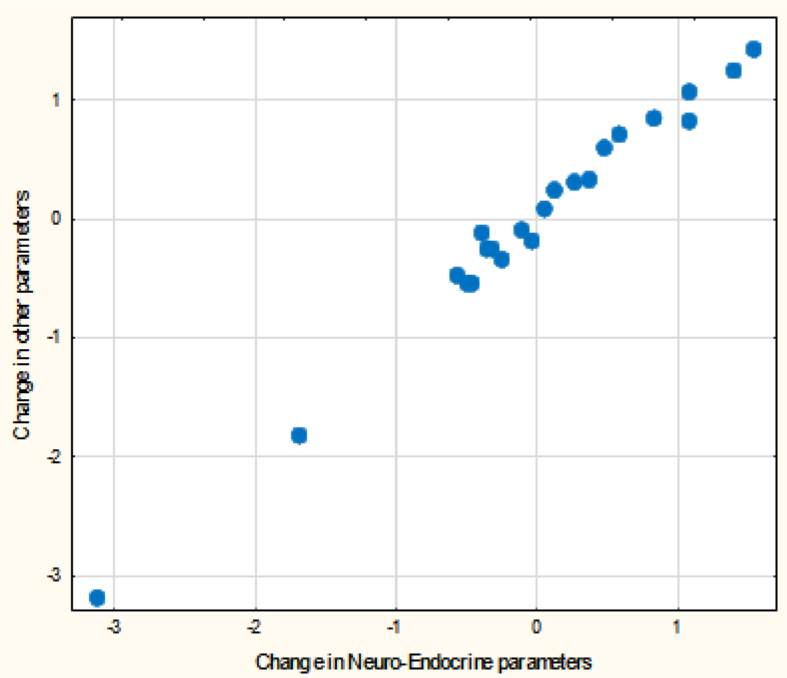
R=0,997; R^2=0,995; $\chi^2_{(91)}$=155; p<10^{-4}; Λ Prime<10^{-6}

Fig. 1. Scatterplot of canonical correlation between change in Neuro-Endocrine (X-line) and Immune, Microbiota and Metabolic (Y-line) parameters. First pair of Roots

The factor structure of the neuro-endocrine root of the second pair (Table 3) is supplemented by beta-rhythm-generating nerve structures, probably [33] of the right prefrontal cortex and aldosterone. Changes in this constellation of neuroendocrine parameters determine changes in the parameters of cholekinetics, metabolism, microbiota, immunity, and diastolic pressure by 98,6% (Fig. 2).

Table 3. Factor loads on the second pair of canonical roots

Neuro-Endocrine Variables	R 2
F8-β PSD, %	0,710
T5 β, PSD, $\mu V^2/Hz$	0,674
Cortisol	0,669
LF, %	0,307
Aldosterone	0,125
C3-δ PSD, $\mu V^2/Hz$	-0,574
VLF, %	-0,189
Dependent Variables	**R 2**
Cholecystokinetic Index, units	0,615
Uric acid Excretion, mM/24 h	0,216
Leukocyturia, lgLeu/L	0,163
Blood Pressure Diastolic, mmHg	0,130
Creatinine Excretion, mM/24 h	0,103
Sodium Excretion, mM/24 h	-0,466
Monocytes, %	-0,330
Escherichia coli feces, lgCFU/g	-0,272
Ig M Serum, g/L	-0,238
Ig G Serum, g/L	-0,209
$CD3^+$ active T-Lymphocytes, %	-0,197
Killing Index vs E. coli, %	-0,182



R=0,993; R^2=0,986; $\chi^2_{(72)}$=100; p=0,017; Λ Prime<10^{-4}

Fig. 2. Scatterplot of canonical correlation between change in Neuro-Endocrine (X-line) and Immune, Microbiota and Metabolic (Y-line) parameters. Second pair of Roots

Given the presence of chronic cholecystitis in the observed contingent, the mechanism of the normalizing effect of mineral waters on the reduced evacuation function of the gallbladder, estimated by the cholecystokinetic index, deserves a separate analysis.

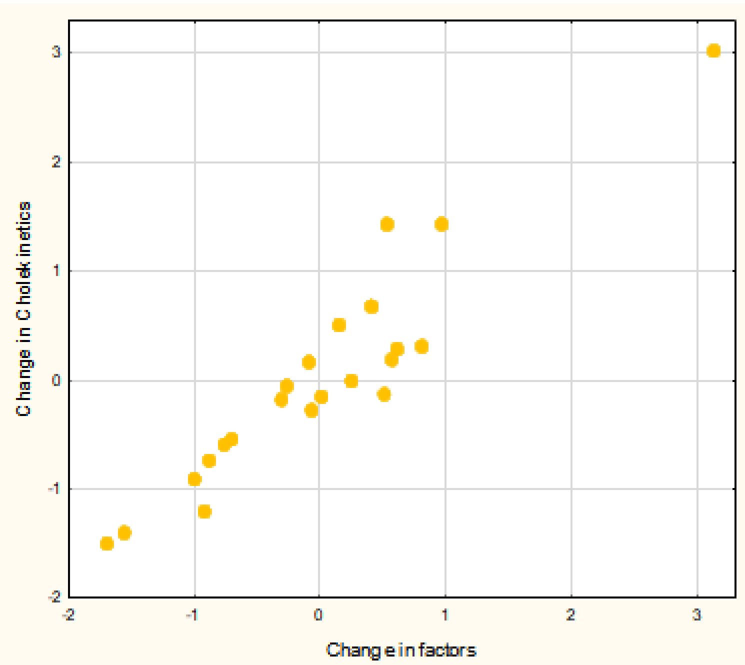
The correlations between the dynamics of the cholecystokinetic index and the discriminant variables were first screened. After that, a regression model was created by step-by-step excluding variables until the maximum Adjusted R^2 value was reached (Table 4).

Table 4. Regression Summary for change in Cholecystokinetics index
$R=0,939$; $R^2=0,882$; Adjusted $R^2=0,794$; $F_{(9,1)}=10,0$; $p=0,0003$

N=22		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(12)}$	p-level
Variables	r		Intercpt	239	35,5	6,74	10^{-4}
Triiodothyronine, nM/L	**0,48**	-0,306	0,160	-80,13	42,06	-1,90	0,081
T4-β PSD, %	**0,42**	0,519	0,158	4,586	1,393	3,29	0,006
Entropy T4	**0,42**	0,564	0,172	746,4	227,0	3,29	0,006
Entropy O2	**0,40**	0,638	0,269	541,6	228,7	2,37	0,036
Entropy F7	**0,38**	-0,570	0,237	-381,8	158,8	-2,40	0,033
LD Cholesterol, mM/L	**0,32**	-0,254	0,174	-33,66	23,08	-1,46	0,170
Glucose Plasma, mM/L	**-0,55**	-0,272	0,146	-39,63	21,33	-1,86	0,088
Cl Urine, mM/L	**-0,55**	-0,653	0,170	-2,285	0,595	-3,84	0,002
Mg Urine, mM/L	**-0,33**	-0,230	0,124	-58,91	31,82	-1,85	0,089

It was stated that the dynamics of the cholecystokinetic index is positively related to changes in plasma triiodothyronine levels, activity of beta-rhythm-generating nerve structures projected at the T4 locus (probably right amygdala [31] and/or temporal gyrus cortex [33]), entropy EEG in loci T4, O2 and F7, as well as low-density lipoprotein cholesterol. In contrast, changes in glycemia and urinary chloride and magnesium concentrations are negatively related to cholecystokinetic index dynamics.

Taken together, changes in these factors due to mineral waters determine changes in cholekinetics by 88% (Fig. 3).



$R=0,939$; $R^2=0,882$; $\chi^2_{(9)}=33$; $p=0,0001$; Λ Prime=0,118

Fig. 3. Scatterplot of canonical correlation between change in Neuro-Endocrine and Metabolic (X-line) and Cholecystokinetics (Y-line) parameters

CONCLUSION

"Myroslava" and "Khrystyna" mineral waters have both similar and different effects on the body of rats [1,11,12,24] and humans [8,13,14,25]. It is important that the differences are manifested not only in the severity of changes in the registered parameters, but also in their direction. Since the chemical composition of both mineral waters is qualitatively identical, the difference in physiological effects is due, apparently, to their total mineralization. The primary effects of mineral waters are the modulation of the activity of the structures of the central and autonomic nervous and endocrine systems, which, in turn, have a regulatory modulating effect on the immune system, microbiota, metabolism, cholekinetics and blood pressure.

The obtained results fit well into the concept of functional-metabolic continuum [7] and neuroendocrine-immune complex [9,26] as well as ambivalence-equilibratory character of influence of curative water on organism of human [3].

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ACCORDANCE TO ETHICS STANDARDS

Tests in patients are carried out in accordance with positions of Helsinki Declaration 1975, revised and complemented in 2002, and directive of National Committee on ethics of scientific researches. During realization of tests from all participants the informed consent is got and used all measures for providing of anonymity of participants.

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